Meiotic recombination within plant centromeres

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Abstract

Meiosis is a conserved eukaryotic cell division that increases genetic diversity in sexual populations. During meiosis homologous chromosomes pair and undergo recombination that can result in reciprocal genetic exchange, termed crossover. The frequency of crossover is highly variable along chromosomes, with hot spots and cold spots. For example, the centromeres that contain the kinetochore, which attach chromosomes to the microtubular spindle, are crossover cold spots. Plant centromeres typically consist of large tandemly repeated arrays of satellite sequences and retrotransposons, a subset of which assemble CENH3-variant nucleosomes, which bind to kinetochore proteins. Although crossovers are suppressed in centromeres, there is abundant evidence for gene conversion and homologous recombination between repeats, which plays a role in satellite array change. We review the evidence for recombination within plant centromeres and the implications for satellite sequence evolution. We speculate on the genetic and epigenetic features of centromeres that may influence meiotic recombination in these regions. We also highlight unresolved questions relating to centromere function and sequence change and how the advent of new technologies promises to provide insights.

Keywords: Meiosis, centromeres, recombination, DSB, crossover, CENH3, H3K9me2, DNA methylation, satellites.

Main text:

1. Meiosis, centromeres and recombination:

Meiosis is a specialized eukaryotic cell division that produces haploid cells, via one round of DNA replication and two rounds of chromosome segregation [1]. Following chromosome replication, sister chromatids are held together by cohesin rings [2]. Unlike during mitosis, meiotic homologous chromosomes pair and synapse to form bivalents (Fig. 1A) [1]. During meiotic prophase I chromosomes undergo DNA double strand breaks (DSBs) that may be repaired using a homolog to form reciprocal crossovers [1,3]. At the end of the first meiotic division, homologous chromosomes segregate, which is achieved by mono-orientation of sister chromatid kinetochores towards the same cell pole (Fig. 1A) [4,5]. Crossovers form a physical link (chiasmata) between the homologs, which together with sister cohesion, are required for balanced segregation [1]. Cohesin is lost from the chromosome arms at the end of meiosis I, but is protected at the centromeres, until it is lost during meiosis II, allowing sister chromatids to segregate into haploid daughter cells [1]. Hence, meiosis involves specialized regulation of chromosome cohesion, interhomolog recombination and centromere behavior in order to produce genetically diverse haploid daughter cells.

Meiotic DSBs form in plants via a conserved SPO11-1/SPO11-2/MTOPVIB topoisomerase-like complex [6*,7*]. SPO11 proteins become covalently bound to DSB 5′-ends during catalysis [8].

Endonuclease followed by exonuclease activities remove SPO11 and initiate resection to produce 3′-overhanging single stranded DNA (ssDNA) [9]. Meiotic ssDNA is bound by the RecA homologs RAD51 and DMC1, which promotes strand invasion of a sister chromatid or a homologous chromosome [1,9]. Interhomolog joint molecules form via displacement loops (D-loops), following which the invading 3′-end may undergo template driven synthesis [1,3]. At this stage extended D-loops may be dissolved by anti-crossover activities and the ssDNA can return to its parent chromosome and be repaired as a non-crossover [1,3]. Hence, template-synthesis over polymorphic sites can cause gene conversion and 3:1 inheritance through meiosis [1]. In Arabidopsis, ~100-200 DSB-associated foci are cytologically observed along the chromosome axis during early prophase I, whereas only ~10 DSBs mature into crossovers [1,6*]. The repair of the remaining DSBs occurs either via the non-crossover pathway, or using a sister chromatid [1]. Measurement of meiotic gene conversion using transgenes or sequencing of recombinant Arabidopsis plants has defined rates in the range of $1.1–8.8\times10^{-5}$ sites per meiosis [10–12]. Evidence for intersister repair comes from analysis of haploid meiosis, where recombination is RAD51 and REC8 dependent, but DMC1 independent [13].

In plants, the conserved Class I 'ZMM' pathway provides the major activity for crossover formation [1]. This pathway acts to stabilize interhomolog joint molecules and promote crossover resolution of double Holliday junction (dHJ) intermediates [1,3]. Within plants, the ZMM pathway includes the MER3 helicase, HEI10 E3 ligase, ZIP4, SHORTAGE IN CHIASMATA1 (SHOC1), PARTING DANCERS (PTD), the MSH4-MSH5 $MutS_{\gamma}$ and the MLH1-MLH3 $MutL_{\gamma}$ heterodimers [1]. A minority of crossovers are formed by the Class II pathway(s), that involve structure specific endonucleases, including MUS81 [1]. A key distinction between Class I and II crossovers, is that the former show interference, meaning that crossovers are more widely spaced than expected by chance [1]. In Arabidopsis, acting in opposition to these pro-crossover activities are partially redundant anti-crossover pathways, including (i) FANCM, MHF1 and MHF2, (ii) FIDGETIN-LIKE-1 (FIGL1) and FIGL1 INTERACTING PROTEIN (FLIP) and (iii) RECQ4A, RECQ4B, RMI1 and TOPOISOMERASE3α, which act to disassemble joint molecules or by regulating strand invasion [1,14]. In plants the combined outcome of the competing pro- and anti-crossover pathways is that most chromosomes experience between 1-3 crossovers, irrespective of genome size, and in divergent positions between independent meioses.

Meiotic DSB and crossover frequency tend to be non-homogenously distributed along chromosomes, with narrow ~kilobase hot spots that show 10-100 fold greater recombination than the background rate [15]. Equally, large chromosome regions are recombination cold spots, notably including the centromeres [16*–19] (Fig. 1). For example, many important crop plant species show pronounced distal skews of crossover frequency towards sub-telomeric regions, away from the centromeres [17*,18,20,21]. One reason for recombination-suppression within centromeres is that proximal crossovers have been associated with higher rates of aneuploidy in fungi and animals, including in human trisomy [22]. In this review, we examine the genetic and epigenetic organization of plant centromeres and how this relates to patterns of meiotic recombination. We discuss the potential roles that recombination may play in driving centromere evolution. Finally, we consider how new sequencing technologies will advance the study of plant centromeres and some of the outstanding questions to be addressed.

2. Genetic and epigenetic features of plant centromeres:

The primary function of centromeres is to assemble the kinetochore, a multi-megadalton protein complex that connects chromosomes to spindle microtubules during mitotic and meiotic segregation (Fig. 1A) [23]. Kinetochore position is epigenetically determined by nucleosomes

containing the histone 3 variant CENP-A/CENH3 [23–25]. Mammalian CENP-A nucleosomes directly bind the core kinetochore proteins CENP-N and CENP-C [23], and CENP-C plays a conserved role in maize [26]. CENP proteins form the constitutive centromere-associated network (CCAN), which further interacts with the KNL1-Mis12-Ndc80 (KMN) network to bind the spindle microtubules [23]. Homologs of the KMN network have been shown to play a conserved role in plant centromeres and kinetochore attachment to spindle microtubules [4,27–29].

CENH3 possesses a histone-fold domain that is similar to histone 3, but its N-terminal tail is highly divergent [24,30]. The histone fold domain is required to target CENH3/CENP-A to the centromere [23,31–33]. In Arabidopsis, transgenes expressing a GFP-tailswap CENH3 protein, with the N-terminus exchanged with histone 3.3, are able to complement *cenh3* lethality [28*]. However, GFP-tailswap CENH3 is not loaded during meiosis, causing sterility [28*]. This implies meiosis-specific CENH3 loading mechanisms in plants that require the N-terminal tail. This is also consistent with observations of biphasic CENH3 loading during rye meiosis [34]. Despite the conserved function of CENH3/CENP-A remarkable levels of sequence divergence between species are observed, which may reflect meiotic drive caused by genetic conflicts [35].

In most plants, the DNA sequences underlying the centromeres consist of megabase arrays of tandemly repeated satellite sequences, interspersed with Gypsy LTR retrotransposons [36–39]. For example, Arabidopsis centromeres consist of 180 bp *CEN180* satellite arrays interspersed with *ATHILA* retrotransposons (Fig. 1C and 2) [19,37*]. Satellite monomers are frequently of similar length to that occupied by a nucleosome (~147 bp) For example, Arabidopsis *CEN180*=180 nt, maize *CentC*=156 nt and rice *CentO*=155 nt, although monomer sequences are poorly conserved beyond 50 million years of divergence [37*,39–41]. CENH3 occupancy mapped by ChIP-seq typically shows enrichment on a subset of the centromeric satellite arrays and retrotransposons [37*–39,42–44]. Many Gypsy LTR retrotransposons that predominate in plant centromeres belong to the Chromovirus family, which are typified by integrase-chromodomain fusions [36]. Interestingly, such chromodomains are sufficient to target heterochromatin in plants and fungi [45*]. However, it is noteworthy that the Tal1 *COPIA* retrotransposon from *Arabidopsis lyrata* shows a strong preference for centromeric insertion when introduced into *A.thaliana*, despite lacking an integrase-chromodomain [46].

The high divergence of satellite and *CENH3* sequences between species suggests meiotic drive and potentially co-evolution [35]. However, transformation of Arabidopsis *cenh3* mutants with *CENH3* from other species (*A.arenosa*, *L.oleraceum*, *B.rapa*, *Z.mays* and *V.vinifera*) results in complementation and normal centromere localization, measured via immunolocalization and ChIP [37*,47,48]. Cross species centromere loading of CENH3 has also been observed in oat-maize addition lines and in barley hybrids [49,50]. This shows that CENH3 loading can occur on divergent satellite sequences. However, following crossing of Arabidopsis *cenh3* complemented lines with wild type, the resulting progeny include haploids and anueploids, due to the chromosomes loaded with the variant CENH3 being lost early during embryogenesis [47,51*]. CENH3-mediated genome elimination in Arabidopsis associates with formation of micronuclei in embryonic cells, chromosome shattering and repair via non-homologous end joining (NHEJ) [52*], which is likely related to the phenomenon of chromothripsis seen in cancer [53]. CENH3-mediated genome elimination demonstrates the potent effect that centromere variation can exert on chromosome transmission and has powerful potential applications in plant breeding [48,51*].

A classical demonstration of the epigenetic flexibility of centromeres, is via formation of neo-centromeres, for example following deletion of the endogenous centromere [54]. Neo-centromeres have been found in diverse species and may form on unique or repeated

sequences that lack centromeric satellites and retrotransposons [55*,56]. This implies that established centromeres normally suppress formation of incipient neocentromeres. Indeed, this was directly seen in maize dicentric chromosomes, where one of the former centromeres is suppressed [57]. Centromere location is typically stable in maize, although some drift of CENH3 domains mapped by ChIP-seq between maize siblings occurs, over a distance of ~100 kb [55*]. In oat-maize addition lines, that carry a single maize chromosome combined with the oat genome, the maize centromere expands to twice the size, and in some cases relocates [58*]. This indicates *trans* modification of maize centromere organization by the oat chromosomes. There are also notable departures from monocentric architecture in holocentric and polycentric plants, where CENH3 occupancy and kinetochores are distributed along the entire length of the chromosomes or at multiple locations, respectively [59,60].

A further common feature of most plant centromeres is enrichment of transposable elements (TEs) and other repeats, flanking the centromeric satellite arrays, termed pericentromeric heterochromatin (Fig. 1B) [61]. Plant heterochromatin is epigenetically modified with an array of chromatin modifications including CG, CHG and CHH DNA methylation, histone H3K9me2, H3K27me1 and histone variant H2A.W [62–65]. These marks contribute to increased nucleosome density, cytological condensation, A/B compartment structure, late-replication, suppressed meiotic recombination, suppressed RNA polymerase II transcription and elevated RNA polymerase IV and V transcription, in these regions [16*,62–67]. Mutants that disrupt heterochromatin cause varying changes to transcription and recombination in the pericentromeres [16*,62–66]. However, to date plant heterochromatin mutants have not been observed to show defects in chromosome segregation [61]. In contrast, disruption of pericentromeric heterochromatin in fission yeast causes loss of centromeric cohesion and aneuploidy [68]. However, as redundant pathways maintain plant heterochromatin, removal of multiple epigenetic marks simultaneously may be necessary to influence centromere function and chromosome segregation.

3. Suppression of meiotic recombination in plant centromeres:

The totality of factors that limit crossover formation within and in proximity to centromeres remains unclear. One possibility could be restriction of the initial precursor DSBs. During catalysis SPO11-1 becomes covalently bound to target site oligonucleotides, which can be sequenced to generate maps of meiotic DSBs [16*,69]. For example, Arabidopsis SPO11-1-oligonucleotides show relative suppression within pericentromeric heterochromatin (Fig. 1B) [16*]. In contrast, SPO11-1 ChIP-seq shows enrichment in Arabidopsis pericentromeric heterochromatin [70]. This implies that DSB formation by SPO11-1 is not limited by its presence on the meiotic axis, and that other steps are required to activate recombination. This is in agreement with observations in budding yeast whose centromeres are DSB suppressed, even when Spo11 is artificially tethered there [71*,72]. A second broad possibility is that crossover repair in centromeres could be suppressed downstream of DSB formation. For example, meiotic DSB repair within the centromeres may favour inter-sister or non-crossover pathways, instead of crossover. Support for this model is provided in maize centromeres, where meiotic DSB activity, measured by RAD51 foci or ChIP-seq signal or gene conversion, has been detected, yet crossovers are absent [73*,74*]. We consider three mechanisms with the potential to suppress meiotic DSBs, or downstream crossover repair, in the centromeres: (i) epigenetic factors, including histone modifications and DNA methylation, (ii) genetic variation, including inter-homolog structural polymorphism, and (iii) non-histone chromosomal proteins, including the kinetochore and cohesin.

The role of heterochromatin in suppression of meiotic crossover has been studied in Arabidopsis. For example, RNA directed DNA methylation (RdDM) targeted to crossover hot spots located in euchromatin caused acquisition of dense CG, CHG and CHH DNA methylation, H3K9me2, higher nucleosome density and suppressed crossovers [75*]. However, at the chromosome-scale, loss of DNA methylation in CG (e.g. *met1*) versus non-CG (e.g. *kryptonite/suvh4 suvh5 suvh6*) contexts has different effects on centomere-proximal crossovers [16*,64*,75*]. Despite both classes of mutant showing increased SPO11-1-oligos in the centromeric and pericentromeric regions, CG mutants show decreased crossovers and non-CG mutants show increased crossovers [16*,64*,75*]. Importantly, H3K9me2 remains in CG mutant centromeres [76], but is reduced or absent in non-CG mutants [63,64*]. Hence, H3K9me2 may suppress crossover maturation in *met1* centromeres, despite increased DSBs. This leads to a model where DSBs may be widespread throughout heterochromatin, and perhaps centromeres, but are suppressed from crossover maturation by epigenetic marks, including H3K9me2. Suppression of centromeric crossovers in hybrid plants may also be attributed to structural variation in satellites arrays, including inversions [77,78].

Evidence exists for non-histone chromosomal proteins regulating crossovers in centromeres. For example, the kinetochore CCAN/Ctf19 complex suppresses recombination in vicinity of the budding yeast centromeres, in addition to promoting cohesin loading [71*,79]. As cohesins favour DSB repair with sister chromatids rather than homologs [80,81], pericentromeric cohesin enrichment could thereby limit interhomolog recombination. Indeed, ChIP-seq of REC8 (the meiosis-specific α-kleisin cohesin subunit) in Arabidopsis, has shown enrichment within pericentromeres, which negatively correlates with meiotic DSBs and crossovers [70]. In fission yeast, a specific cohesin complex, Rec8-Psc3, acts to repress meiotic recombination in the pericentromeres [82]. Pericentromeric enrichment of cohesin in fission yeast is also dependent upon H3K9 methylation and heterochromatin protein Swi6 [68,83,84]. In contrast, in mice centromeric cohesion is maintained in *suv39h-1 suv39h-2* H3K9 methylation mutants during mitosis, although remodeling of cohesin occupancy occurs on specific repeats [85,86]. In Arabidopsis loss of H3K9me2 and non-CG DNA methylation in *kyp suvh5 suvh6* triple mutants causes remodeling of REC8, which is associated with gain of meiotic recombination in repeats, although as in mice, centromere cohesion is maintained [64*,70].

4. Evidence for recombination in plant centromeres:

Suppression of meiotic recombination in centromeres is a conserved phenomenon [22]. However, the evolution of tandem arrays of satellite repeats, which often show higher order duplications (e.g. Fig. 2), implies that DNA repair and recombination has nevertheless occurred. Possible recombination-dependent mechanisms for satellite expansion or contraction include, (i) somatic homologous and non-homologous recombination, (ii) unequal meiotic crossover and (iii) meiotic gene conversion. Interspersed centromeric retroelements may also play a role in generating sequence change, acting either as recombination substrates, or via transpositional effects [87]. Recombination-independent mechanisms, such as replication slippage, could also play a role [88]. We will consider the evidence for these different modes of recombination and their potential to drive satellite duplication in plant centromeres.

Somatic homologous recombination (HR) in plants has been studied using transgenes, where homologous recombination between *GUS* sequences on the same or different T-DNAs restores β-glucuronidase activity [89,90]. Recombination measured using these assays shows the classic features of HR, including a suppressive effect caused by substrate divergence and RAD51-dependence [89,90]. Hence, it is possible that somatic DSBs occurring in the satellite arrays could be repaired non-allelically via HR pathways, which could cause monomer

duplications and deletions, or higher order changes. Evidence for the action of non-homologous pathways, including microhomology mediated DSB repair, also exists in maize centromeres [78]. For such somatic changes to have transgenerational significance, the mutations must occur in a clone of cells that leads to germ line differentiation. For example, tomato site-specific induced DSBs have been shown to cause somatic HR mediated repair, which led to genetic changes transmitted to progeny [91].

A second broad possibility is that meiotic recombination causes changes to the satellite arrays, which would transmit between generations via the gametes. For example, following SPO11-1 dependent DSB formation, resection and strand invasion, repeat sequences may misalign with non-allelic repeats. If crossover proceeds in this situation then unequal exchange may occur, creating duplications or deletions of the associated repeats. For example, unequal crossover has also been proposed to generate structural diversity in plant disease resistance gene clusters [92,93]. Analysis of rice and maize centromere sequences has revealed segmental duplications of CentO/CentC satellite repeats consistent with unequal recombination [78,94]. However, direct observation of unequal crossover in plant satellite repeats is so far lacking, and crossovers are typically suppressed in the centromeres (Fig. 1C) [16*–18,20,74*]. A further possibility is meiotic gene conversion. As discussed earlier, the majority of meiotic inter-homolog strand invasion events are dissolved via anti-crossover activities, in which case the ssDNA returns to the parent homolog and is repaired as a non-crossover [1]. Supporting a role of meiotic gene conversion, genetic mapping within maize centromeres has revealed conversion of *CRM* retrotransposons, but an absence of meiotic crossovers [74*]. Further study of plant centromere sequence stability in wild type and mutant backgrounds will be required to investigate the contributions of these varying recombination pathways.

5. New technologies and open questions

A major challenge to studying centromeres is that the megabase arrays of satellites remain difficult to sequence and assemble. However, new DNA sequencing and analysis technologies promise to make this more widely achievable. First, optical mapping techniques allow genome-wide physical assemblies to be obtained [95]. For example, Bionano technology allows megabase length DNA molecules to be fluorescently labeled at restriction sites, linearized and directly visualized during microfluidic separation. This generates a genome-wide restriction map, that can be used to anchor and orientate sequence contigs [95]. Second, high throughput sequencing technologies that provide longer read lengths (kilobase to megabase), including Pacific Biosystems, Oxford Nanopore and 10x Genomics, promise to dramatically improve centromere assemblies. These technologies will allow satellite array dynamics to be investigated within and between generations, in order to address the role of somatic versus germline homologous recombination. A range of mutations are available in model plant species that disrupt recombination, cohesin, chromatin and the kinetochore. Assembly of centromere sequences in these mutants, using new technologies may allow effects on satellite sequence stability to be tested.

Recombination suppression in the centromeres is observed in the majority of eukaryotes [16*–19,22]. Candidate factors that may repress meiotic DSBs, or promote inter-sister and non-crossover repair, in the centromeres, include chromatin, cohesin, kinetochore occupancy or structural heterozygosity. Interestingly, the *SMC4* condensin gene was genetically identified as playing a role in heterochromatic silencing via DNA methylation in Arabidopsis [96*]. Hence, interactions between cohesin, condensin and chromatin, and their roles in shaping meiotic DSB and crossover frequency within plant centromeres will be interesting to further explore. It is also possible that CENH3 may contribute to suppression of meiotic recombination in plant genomes,

although this remains untested. The environment may influence levels of recombination close to the centromeres. For example, elevated temperature (25°C or 30°C) increased crossovers genome-wide in barley and caused a shift towards interstitial and centromere-proximal regions [97]. Interestingly, in Brassica allotriploid AAC hybrids, a global recombination increase occurs in the A genome, including in centromere-proximal regions, compared to AA diploids, which may imply *trans* modification by the C genome [98].

Ultimately, a detailed understanding of plant centromere DNA sequence composition and chromatin promises to provide insight into their evolutionary dynamics. Satellite sequences show rapid divergence between species and evidence of concerted change across chromosomes. In some cases the youngest satellites correspond to CENH3/CENP-A occupied sequences, with older satellites and transposon sequences located distally to the kinetochore [37*,38,99,100]. Gene conversion is one mechanism whereby concerted evolution and homogenization of sequences may occur [74*,101]. Targeted transposition may further allow centromeres on different chromosomes to acquire the same repeats [87]. *Trans* modifier loci can also influence centromere behavior. For example, the maize Abnormal chromosome 10 (Ab10) locus causes heterochromatic knobs to acquire 'neocentromere' identity and migrate to the cell poles faster than the established centromeres [102], although interestingly the neocentromere-knobs do not stain for CENP-C [26]. Ab10 can thus cause meiotic drive in knob-linked regions and was recently identified as a cluster of kinesin genes [103*]. It will be interesting to further define the role that recombination plays in driving evolution of satellite arrays and similar centromere-modifier loci, and thereby influencing the potential for genetic conflicts during meiosis.

Figure Legends

Figure 1. Meiotic recombination is suppressed in Arabidopsis centromeres. A. A schematic diagram of *Arabidopsis thaliana* chromosome 1 at pachytene is shown. Replicated sister chromatids are tethered by cohesin rings (red). Homologous chromosomes are labeled m and p, and joined via the synaptonemal complex (SC, green). MLH1 and HEI10 (blue) label large foci/nodules that correspond to Class I crossover sites. In the centromeres, H3 (blue) is replaced with CENH3-containing nucleosomes. Spindle microtubules (pink) attach to CENH3 chromatin, with sister chromatid kinetochores mono-orientated towards the same cell pole. Diagram is not to scale. **B.** Meiotic DSB frequency, measured by SPO11-1-oligonucleotides, plotted along chromosome 1 (red) [16*], plotted alongside DNA methylation (blue) [75*]. The position of the centromeric assembly gap is indicated by the vertical dotted line. **C.** As for B, but showing meiotic crossover frequency (red), measured by sequencing Col×Ler F_2 plants [16*], compared to Gypsy LTR (blue) and CACTA/EnSpm (pink) transposon density. Matches to the *CEN180* consensus sequence are shown along the x-axis, colored according to forward (red) or reverse (blue) strand mapping. Beneath is a representation of the estimated 9 Mb of unassembled centromere sequence, which is thought to consist predominantly of *CEN180* satellites [104].

Figure 2. Sequence composition of the *Arabidopsis thaliana* centromeric regions. A. Annotation of a 234 kilobase region of chromosome 1 from the TAIR10 assembly that is located in proximity to the centromere. Sequences are colored according to homology with *CEN180* satellites (yellow), Gypsy LTR retrotransposons (red) and CACTA/EnSpm DNA transposons (pink). **B.** Dot plot analysis of the region shown in A, where shading indicates pairwise sequence identity, using word sizes of 15 and 130 nucleotides. The colored shading on the axes matches the sequence annotation shown in A.

Acknowledgements:
We thank Andrew Tock for input on Figure 1 and the reviewers for useful feedback. We acknowledge grant support from the ERC (PoC HEIREC), EMBO (Long Term Fellowship to JBF), Marie-Curie MEICOM ITN (PW) and ERC CoG SynthHotSpot (IRH) for support.

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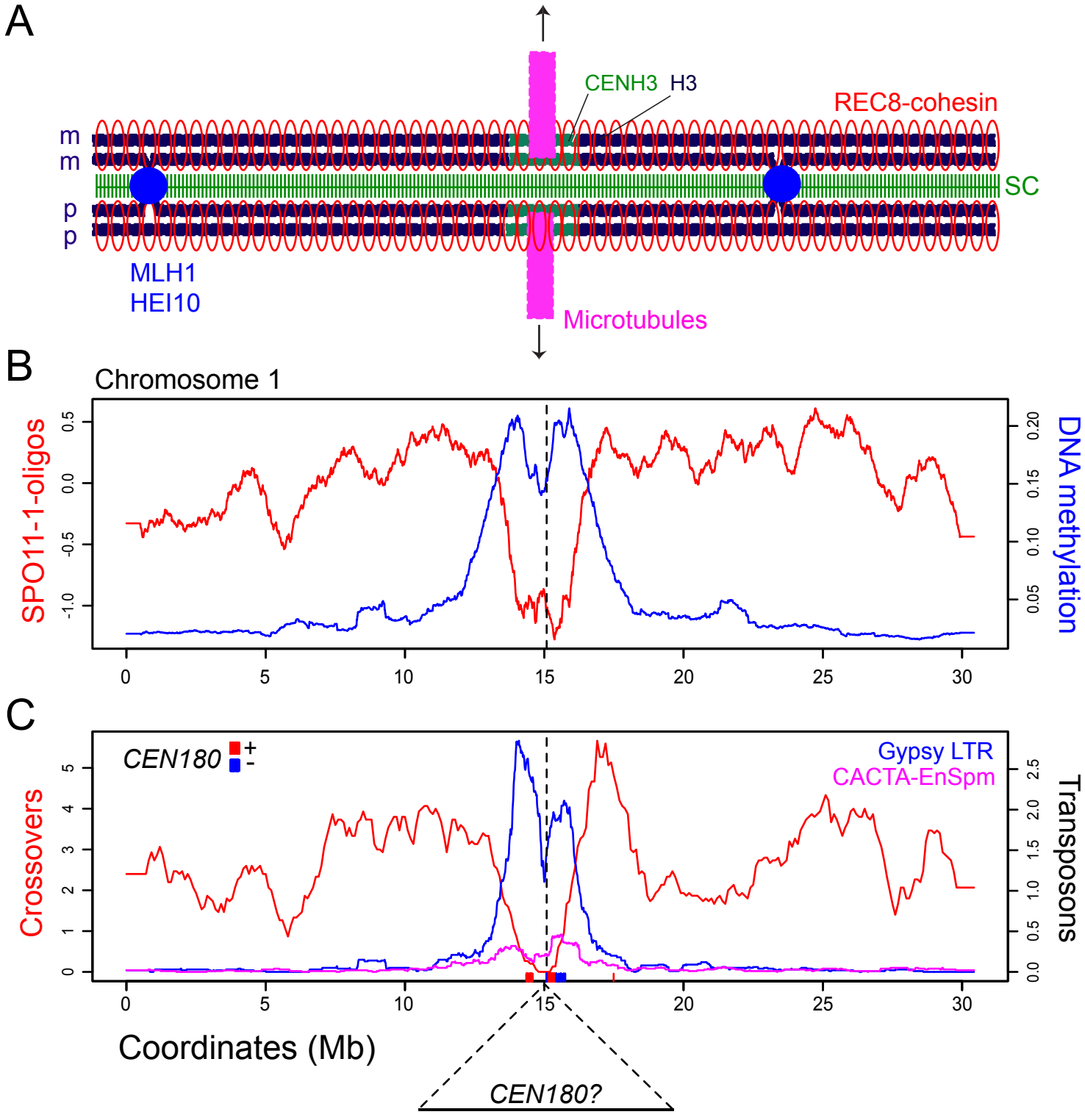
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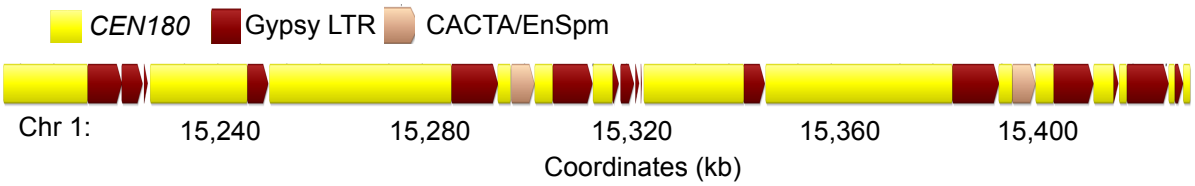
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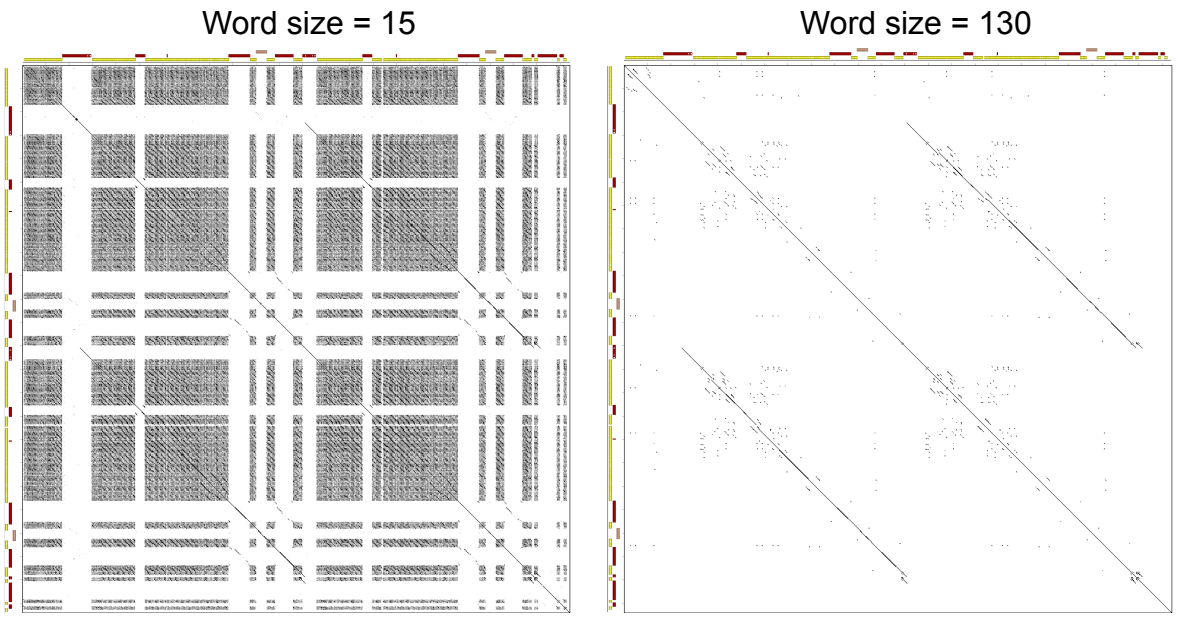
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